

Streptogramins and a process for preparing
streptogramins by mutasynthesis

The present invention relates principally to novel compounds which are related to the group B streptogramins, and to a process for preparing streptogramins by mutasynthesis. It also relates to novel genes which are involved in the biosynthesis of precursors of the group B streptogramins, and to their uses.

10 The streptogramins form a homogeneous group of antibiotics consisting of an association of two types of chemically different molecules; on the one hand polyunsaturated macrolactones (group A components) and, on the other hand, depsipeptides (group B
15 components). This group comprises numerous antibiotics which are known under different names according to their origin and includes pristinamycins, mikamycins and virginiamycins (Cocito 1979, 1983).

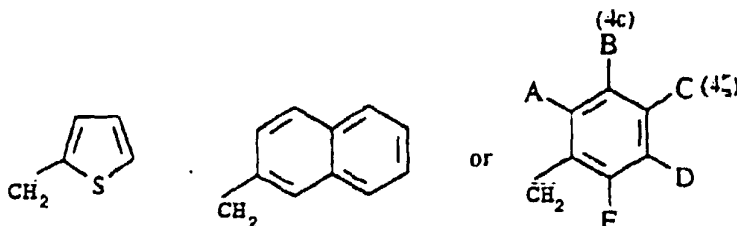
The A and B components have a synergistic
20 antibacterial activity which can amount to 100 times that of the separate components and which, contrary to that of each component, is bactericidal (Cocito 1979). This activity is more particularly effective against Gram positive bacteria such as Staphylococci and
25 Streptococci (Cocito 1979, Videau 1982). Components A and B inhibit protein synthesis by binding to the 50S

- R_2 and R_4 represent, independently of each other, a hydrogen atom or a methyl group,

- R_3 represents a hydrogen atom or a hydroxyl group,

5 - X represents a CO, CHOH or CH_2 group, and

- R_1 represents:



with

- for the meta derivatives:

A, C, D and E representing a hydrogen atom, and

10 B being able to represent

- a halogen, and preferably a fluorine atom,

✓ - a monoalkylamino or dialkylamino group,

with alkyl preferably representing a methyl or ethyl group,

15 - an ether group; more particularly an OR group with R being preferably selected from among the methyl, ethyl, trifluoromethyl and allyl groups,

- a thioether group, preferably represented by an alkylthio group with alkyl preferably

20 representing a methyl group,

- a C₁ to C₃ alkyl group, or

- a trihalogenomethyl group, preferably trifluoromethyl

- for the para derivatives

A, B, D and E representing a hydrogen atom, and
C being able to represent:

- a halogen,

5 - an NR_1R_2 group with R_1 and R_2 representing,
independently of each other, a group selected from
among

- hydrogen,

✓ - a straight-chain or branched C₁ to C₄

10 alkyl group where, when one of the substituents R_1 or R_2 represents a methyl group, the other necessarily represents an ethyl group,

- an alkyl-cycloalkylmethyl group with a C₁ to C₄ cycloalkyl,

- an optionally substituted C₁ to C₆
cycloalkyl group,

- a straight-chain or branched C_1 to C_4 alkenyl group where, when one of the substituents R_1 or R_2 represents an alkenyl group, the other is different

20 from a methyl group or a C3 to C6 cycloalkyl,

- a substituted or unsubstituted N-pyrrolidinyl group,

- an ether group; preferably an OR group with R preferably being selected from among the methyl and ethyl groups, where appropriate substituted by a chlorine atom, or trifluoromethyl and alkenyl groups

- a thioether group, preferably represented by an alkylthio group with alkyl preferably

- an acyl or alkoxycarbonyl group and, more particularly, a COR group with R preferably representing a C₁ to C₃ alkyl group or a C₁ to C₃ alkoxy group,

- a C₁ to C₆ alkyl group which is straight-chain or branched and which is preferably selected from among the methyl, isopropyl and tert-butyl groups,

- an alkylthiomethyl group and, more preferably, a CH_2SR group with R preferably representing a C_1 to C_6 alkyl group,

- an aryl group, preferably a phenyl group,
or

- a trihalogenomethyl group, preferably
15 trifluoromethyl

- for the meta-para disubstituted derivatives:

A, D and E representing a hydrogen atom, and
B being able to represent:

20 - a halogen, preferably a fluorine atom,
 - a monoalkylamino or dialkylamino group with
alkyl preferably representing a methyl or ethyl group,
 - an ether group and preferably an OR group
with R preferably selected from among the methyl, ethyl
and trifluoromethyl groups,

25 - a thioether group and preferably alkylthio
with alkyl preferably r presenting an ethyl group, or

- a C₁ to C₄ alkyl group, and

C b i n g a b l e t o r e p r e s e n t: